# *Chapter 7*
# Newborn Screening for Cystic Fibrosis: A Public Health Response

*Denise R. Green, Scott D. Grosse, Marie Earley, and Joanne Mei*

## What Is Cystic Fibrosis?

**Autosomal recessive**
*Condition manifested only when a gene variant is inherited from each parent.*

Cystic fibrosis (CF) is an **autosomal recessive** genetic disorder that affects approximately 1/3,700 births in the United States (1). People with CF have mutations in both copies of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7. Although more than 1,000 mutations of the *CFTR* gene have been identified, 1 mutation, Δ*F508*, accounts for two-thirds of all *CFTR* mutations worldwide (2,3). CF disrupts the normal functioning of multiple organ systems and can affect the lungs and upper respiratory tract, gastrointestinal tract, pancreas, liver, sweat glands, and genitourinary tract (2). In 2001, the median predicted average age of survival in persons with CF was 33 years (4).

## Why Test Newborns for Cystic Fibrosis?

Early diagnosis of CF by newborn screening can help avoid unnecessary physician visits, hospitalizations, and diagnostic tests, along with the costs and parental anxiety associated with having an ill but undiagnosed newborn, and allow for the early introduction of therapies that have proven to be beneficial (5). The median age at which CF is clinically diagnosed based on signs and symptoms (excluding **meconium ileus**) is 14.5 months, compared with 0.5 months for infants diagnosed by newborn screening (6). Naturally, however, the benefits of newborn screening for CF must be balanced with costs and risks, including those associated with false positive test results.

**Meconium ileus**
*An intestinal obstruction present at birth due to abnormally thick meconium that blocks the passage of stool out of the ileum and into the colon.*

Newborn screening is not the only option for early detection of CF. Professional organizations have endorsed the use of prenatal carrier screening (7); however, preliminary data suggest that ≤20% of pregnant women in the United States receive this type of screening (8). In addition, compared with a 95%-99% sensitivity for newborn CF screening (5), the sensitivity of prenatal screening is ≤78% for the non-Hispanic white population and lower for other racial and ethnic groups (9). *For more information, see Chapter 5, ACCE Reviews of Genetic Tests: BRCA1, BRCA2 and CFTR.*

## Public Health Response

In November 2003, the Centers for Disease Control and Prevention (CDC), along with the Cystic Fibrosis Foundation (CFF), held a workshop to address newborn screening for CF. The three objectives of the workshop were to:

- Review and evaluate the scientific evidence on benefits and risks of newborn screening for CF.
- Review screening, diagnostics, and follow-up concerns in CF newborn screening decision-making.
- Disseminate information about models and best practices for states that choose to adopt newborn screening for CF.

A review of the benefits, harms, and recommendations for implementing newborn screening for CF was published October 15, 2004, in the MMWR Recommendations and Reports, and is summarized in the following text box (5).

### Recommendations

The magnitude of the health benefits from screening for CF is sufficient that states should consider including routine newborn screening for CF in conjunction with systems to ensure access to high-quality care.

- In reaching a decision as to whether to add newborn screening for CF, states should consider available state resources and priorities as well as available national guidelines regarding CF screening, diagnosis, and treatment.
- States that implement newborn screening for CF should collect follow-up data in collaboration with CF care centers and analyze this information to monitor and improve the quality of CF newborn screening. In particular, states should collect, share, and analyze data by using standard protocols to evaluate and optimize laboratory algorithms used to screen for CF and refer for diagnosis. States seeking guidance on optimal laboratory protocols might wish to consult with states having more experience in conducting CF screening of newborns.
- Newborn screening for CF should be accompanied by rigorous infection control practices to minimize the risk to children with CF detected at an early age of acquiring infectious organisms associated with lung disease from older patients. Further research is needed to evaluate and optimize these practices.

- Newborn screening systems should ensure parental and provider education and communication of screening results to primary-care providers in a manner that will ensure prompt referral to diagnostic centers. For CF, these should be centers skilled in providing both sweat tests to young, presymptomatic children with CF and accurate and effective counseling to families, including those with infants identified as carriers. States are recommended to work with each other and with professional organizations and federal agencies to develop approaches to provide newborn screening information to parents during the prenatal and perinatal periods on all conditions, including CF, to facilitate informed choices and appropriate responses to positive screen results.

In addition, a recent editorial published in the journal American Family Physician provided a brief overview of the main findings and recommendations from the MMWR report (10).

## Weighing the Costs and Benefits for Universal Newborn Screening for CF

CF may not fulfill the traditional criteria used to justify universal newborn screening, including the specification that immediate intervention should be available to prevent devastating outcomes. Infants with CF rarely die during the newborn period and do not suffer severe intellectual disability due to a lack of early intervention; however, there is evidence of moderate clinical benefit from early detection of CF. Alternative criteria balancing the benefits and risks of screening need to be considered for disorders such as CF; furthermore, the complex policy decision of whether to adopt screening also requires consideration of costs, resources, and priorities (5).

Two randomized, controlled trials and additional observational studies of newborn screening for CF have reported benefits in terms of improved growth, cognitive outcomes, reduced hospitalizations, and increased survival for subjects diagnosed through CF newborn screening. Evidence of any pulmonary benefit remains uncertain, however, and data are lacking for evaluating effects on health-related quality of life. In addition to the health benefits for children, newborn screening provides potential familial benefits by eliminating the "diagnostic odyssey" that generally precedes clinical diagnosis (e.g., multiple doctor visits, unnecessary tests and hospitalizations, considerable healthcare costs, parental anxiety) (5).

The benefits of newborn screening, however, must be weighed against the risks, including the early acquisition of P. aeruginosa infection by infants exposed in CF

clinics to older children with CF who have active lung infections. Strict infection control practices and separation of asymptomatic infants and children from patients with established disease can reduce early acquisition of P. aeruginosa and other lung infections (11). Careful implementation of state newborn screening programs could limit the number of false-positive results and help facilitate the communication of genetic results to parents to minimize parental anxiety and misunderstanding.

Although no complete cost-effectiveness analysis has been published for newborn CF screening, partial cost data from Wisconsin suggest that screening costs were largely offset by savings from reduced demand for sweat tests and that laboratory screening cost for CF is comparable to other newborn screening tests that are in common use (12).

## Adding CF Screening to Existing Newborn Screening Programs

Professional organizations, including the American College of Medical Genetics (ACMG) (13), the March of Dimes (14), and CFF (15) have recommended that states screen for CF based on the benefits of early diagnosis. As of the end of 2004, the following 10 states had implemented universal newborn screening for CF: Colorado, Florida, Massachusetts, Mississippi, Montana, New Jersey, New York, Oklahoma, South Carolina, Wisconsin, Wyoming. In addition, certain hospitals in three other states collect specimens at hospital discharge for screening by a state public health laboratory (Montana), academic laboratories (Connecticut), or a commercial laboratory (Pennsylvania) (16). Other states are considering adding CF to their existing screening programs.

## Challenges in Implementing CF Screening

The addition of a new test to a newborn screening panel presents many challenges. CF screening programs are complex and should be developed in a deliberate fashion, with attention to the experience of existing programs. For states considering CF newborn screening, these challenges include the following:

- Establish appropriate laboratory protocols and algorithms.
- Implement proper and timely follow-up and facilitate communication of genetic information to parents.

**Analytic validity**
*The ability of a test to accurately and reliably measure a specific analyte or identify a mutation of interest.*

**Clinical validity**
*The ability of a test to accurately and reliably identify individuals who either have or will have the disorder or phenotype of interest.*

## Laboratory Implementation Issues

Laboratory implementation for CF screening should consider the testing algorithms to be used, the **analytic validity** and **clinical validity** of the testing, and the laboratory (state, private, or academic) that will perform the testing.

Plasma concentrations of immunoreactive trypsinogen (IRT) are elevated at birth in CF-affected infants and can be easily detected in dried blood spots. When used in conjunction with IRT screening, commercial tests for the most common mutations of the *CFTR* gene can detect most infants with CF (17,18). Screening protocols begin with an initial IRT test conducted on the newborn blood spot specimen collected within 48 hours of birth. In the IRT/IRT protocol, newborns with an elevated IRT in the first test are tested again at approximately 2 weeks of age. If IRT is still elevated, the infant is referred for a sweat test. In other protocols, the second tier test is mutation detection by DNA analysis of the original specimen. States have elected to use either IRT/IRT or IRT/DNA screening protocols. In many newborn screening programs, IRT testing can be added easily, because the technology needed to conduct IRT testing is already in place. Adding DNA testing, however, may require additional equipment and expertise. Some programs may choose to implement all CF screening components within their own laboratories, whereas other programs may choose to partner with academic or private laboratories for some or all of their testing.

To help monitor the analytic validity of CF newborn screening tests, CDC's Newborn Screening Quality Assurance Program has operated a proficiency testing (PT) program for IRT since 2002. During 2003, the program was expanded to add DNA testing for the Δ*F508* mutation. Each quarter, a panel containing positive and negative specimens is distributed to 59 laboratories in 15 countries. CDC is working to develop specimens that can be used with all molecular methods. Newborn screening programs estimate clinical validity by tracking diagnostic outcomes of infants with positive screening results and monitoring the number of missed cases.

## Follow-up and Communication Issues

Protocols and resources for adequate follow-up are essential for children who screen positive for CF. States should ensure that these children are referred in a timely manner to a diagnostic CF care center for sweat testing and genetic counseling. Identifying **carriers** is an unavoidable result of CF newborn screening using IRT/DNA protocols and requires genetic counseling resources for families. Providing more information to parents during both the prenatal and perinatal periods can help state programs alleviate parental anxiety and misunderstanding of CF screening results.

**Carrier**
*A person who has just one copy of a recessive disease-causing gene variant and does not have the disease in question.*

## Conclusion

Newborn screening for CF represents one model for decision making in the public health application of genetic-testing strategies. A decision to adopt population-based screening should be preceded by large-scale pilot studies of screening to

address questions of implementation and to assess impacts, including potential risks. Other programs can apply the lessons learned from these pilot studies in order to ensure that "more good than harm" results from newborn screening for CF (19).

### *References*


1. National Newborn Screening and Genetics Resource Center. National Newborn Screening Report 2000. San Antonio (TX): National Newborn Screening and Genetics Resource Center [online] 2003 [cited 2005 Mar 17]. Available from URL: *http://genes-r-us.uthscsa.edu/resources/newborn/00chapters.html*.

2. Welsh MJ, Ramsey BW, Accurso F, Cutting GR. Cystic fibrosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Basis of Inherited Disease. 8th edition. New York (NY): McGraw-Hill; 2001: 5121-88.

3. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of *CFTR* mutations–correlation with incidence data and application to screening. Hum Mutat 2002;19:575-606.

4. Cystic Fibrosis Foundation. Patient Registry 2001 Annual Report. Bethesda (MD): Cystic Fibrosis Foundation; 2002.

5. Grosse SD, Boyle CA, Botkin JR, Comeau AM, Kharrazi M, Rosenfeld M, et al. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. MMWR 2004;53(RR-13):1-36.

6. Accurso FJ, Sontag MS, Wagener JS. Complications associated with symptomatic diagnosis in infants with cystic fibrosis. Journal of Pediatrics [suppl]. In press.

7. American College of Obstetricians and Gynecologists, and American College of Medical Genetics. Preconception and Prenatal Carrier Screening for Cystic Fibrosis. Clinical and Laboratory Guidelines. Washington (DC): American College of Obstetricians and Gynecologists; 2001.

8. Palomaki GE. Prenatal screening for cystic fibrosis: an early report card. Genet Med 2004;6:115-116.

9. Haddow JE, Palomaki GE, editors. Population-based Prenatal Screening for Cystic Fibrosis via Carrier Testing. ACCE Report. Scarborough (ME): Foundation for Blood Research [online] 2002 [cited 2005 Mar 17]. Available from URL: *http://www.cdc.gov/genomics/info/reports/research/FBR/introduction.pdf*.

10. Grosse SD, Boyle CA, Cordero JF. Newborn screening for cystic fibrosis: recommendations from the Centers for Disease Control and Prevention. American Family Physician 2005;71(8):1482,1487.

11. Saiman L, Siegel J. Infection control recommendations for patients with cystic fibrosis: microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. Infection Control and Hospital Epidemiology 2003;24(suppl 5): S6-52.

12. Lee DS, Rosenberg MA, Peterson A, Makholm L, Hoffman G, Laessig RH, et al. Analysis of the costs of diagnosing cystic fibrosis with a newborn screening program. Journal of Pediatrics 2003;132:617-23.

13. American College of Medical Genetics. HRSA Commissioned Report: Newborn Screening: Toward a Uniform Screening Panel and System [online] [cited 2005 Mar 10]. Available from URL: *http://mchb.hrsa.gov/screening/*.

14. March of Dimes Newborn Screening Recommendations. March of Dimes website [online] [cited 2004 Nov 8]. Available from URL: *http://www.marchofdimes.com/professionals/682_4043.asp*.

15. Cystic Fibrosis Foundation. The CF Foundation Urges All States to Include Newborn Screening for CF in Test Panels. [press release]. North American Cystic Fibrosis Conference, St. Louis; 2004 Oct 15.

16. Wilfond BS, Gollust SE. Policy issues for expanding newborn screening programs: The cystic fibrosis newborn screening experience in the United States. Journal of Pediatrics 2005;146:668-74.

17. Comeau AM, Parad RB, Dorkin HL, Dovey M, Gerstle R, Haver K, et al. Population-based newborn screening for genetic disorders when multiple mutation DNA testing is incorporated: a cystic fibrosis newborn screening model demonstrating increased sensitivity but more carrier detections. Pediatrics 2004;113:1573-81.

18. Rock MJ, Hoffman G, Laessig RH, Kopish GJ, Litsheim TJ, Farrell PM. Newborn screening for cystic fibrosis in Wisconsin: nine years' experience with routine trypsinogen/DNA testing. Journal of Pediatrics [suppl]. In press.

19. Farrell MH, Farrell PM. Newborn screening for cystic fibrosis: ensuring more good than harm. Journal of Pediatrics 2003;133:707-12.